(4)

No. 06-922

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In The Supreme Court of the United States

NUTRACEUTICAL CORPORATION; SOLARAY, INC.,

Petitioners,

v.

ANDREW VON ESCHENBACH, COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION; U.S. FOOD AND DRUG ADMINISTRATION; MICHAEL O. LEAVITT, SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES; DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND THE UNITED STATES OF AMERICA,

Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Tenth Circuit

PETITIONERS' REPLY BRIEF

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PETITIONERS' REPLY BRIEF

The Respondents argue in their brief in opposition that certiorari should be denied because this case hinges on a detailed evaluation of the facts and is therefore devoid of questions of law. Resp. Brief in Opp. at 6, 10. To the contrary, the case raises two quintessentially legal issues that go to the heart of this Court's evolving administrative law jurisprudence, neither of which requires any fact intensive review:

(1) Did the Tenth Circuit disregard the Dietary Supplement Health and Education Act's (DSHEA's) explicit requirement that "[t]he court shall decide any issue under this paragraph on a de novo basis," 21 U.S.C. 342(f)(1), by insisting on applying *Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837, 843-844 (1984), in defiance of the governing statute's command?

(2) May the FDA escape the DSHEA requirement that "[i]n any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated," 21 U.S.C. 342(f)(1), solely by a finding that "[i]n the absence of a clinical indication, it would not be possible to recommend a safe dose of ephedra" (Inchiosa letter, Ref. 84 to FDA Final Rule)?

These questions are of profound significance for the direction of administrative law and the fortunes of an entire industry (indeed, for the freedom of choice of all consumers). By upholding the FDA Final Rule, the Tenth Circuit rejects the above quoted statutory commands. In so doing, it wrongly subjects dietary supplements, unambiguously classified as foods under the Food, Drug and Cosmetic Act (FDCA), 21 USC 321(ff), to the safety and effectiveness review that the FDCA explicitly reserves for drugs, 21

USC 355, without a specific statutory warrant to that effect. This statutory tour de force permits the FDA to ban any dietary ingredient *in toto* as adulterated upon proof of an infinitesimal risk found at a dose level above that recommended by a manufacturer unless the manufacturer proves to FDA's subjective satisfaction that the ingredient produces significant health benefits. Yet in the FDA's benefit equation, through a classic act of legerdemain, the agency refuses to consider proof of any significant *therapeutic* benefit of the dietary ingredient (see *Whitaker v. Thompson*, 353 F.3d 947, 948-949 (D.C. Cir. 2004), reh'g denied, 2004 U.S. App. LEXIS 4617 (D.C. Cir. Mar. 9, 2004), cert. denied, 2004 LEXIS 6703 (U.S. Oct. 12, 2004)) and thus ensures that virtually no health benefit will ever rise to the level of significance needed to counterbalance even an insignificant risk. Consequently, because it is an axiom of toxicology that all foods at some dose level become poisons, FDA's Final Rule is an assumption of extrastatutory authority that permits the agency to deem adulterated (and ban outright) any dietary ingredient it so chooses, even when the dose level recommended to consumers in labeling causes no demonstrable harm whatsoever.

The wholesale reinterpretation of the dietary supplement adulteration provision guts the legal regime put in place by DSHEA; that regime presumes foods, including dietary supplements, safe until FDA proves by a preponderance of the evidence risk of illness or injury at the dose levels recommended in labeling. See S. Rep. 103-410 at 21. Nothing in the statute or its legislative history places on individual manufacturers a duty to prove the health benefits of foods or food ingredients to FDA's satisfaction. Congress did not grant FDA authority to treat dietary supplements like drugs, which the FDA and the Tenth Circuit have done unilaterally; indeed, Congress forbad such treatment. See S. Rep. No. 103-410 at 20 ("The committee

intends that the FDA should regulate dietary supplements as food and not as drugs . . . "). The FDA and the Tenth Circuit's unprecedented decisions have significantly destabilized the dietary supplement marketplace, thereby bringing about the very result that Congress aimed to prevent when it adopted DSHEA. See S. Rep. No. 103-410 at 21-22. As amicus Natural Products Association (the representative of 10,000 natural product producers) explains, "Unless the FDA's standard is reviewed, makers of dietary supplements will be forced to incur much higher expenses in bringing their products to market, and consumers will pay higher costs as a result. Consumer choice will be curtailed, and the longstanding statutory distinction between drugs and dietary supplements (*i.e.*, foods) . . . will be at an end." Brief of Amicus Curiae at 1-2.

ARGUMENT IN REPLY

A. THE DSHEA REQUIRES DE NOVO REVIEW

The FDCA's dietary supplement adulteration provision, 21 USC 342(f)(1), unequivocally states: "The court shall decide any issue under this paragraph on a de novo basis." The Tenth Circuit erred by ruling that "any issue under this paragraph" excluded every case where the FDA declared a dietary supplement adulterated through rulemaking. Contrary to the Respondents' representations to this Court, Resp. Brief in Opp. at 12-13, there is no ambiguity in Congress's sweeping language, "*any* issue under this paragraph" (emphasis added). That language plainly includes every FDA decision on dietary supplement adulteration, regardless of the method the agency uses to make that decision. DSHEA contains no express or implied exception to de novo review for declaring products adulterated through rulemaking. Only by adhering to the plain meaning of the statute can Congress achieve its important

goal of requiring a court to give a fresh look to the factual record before permitting a ban to be imposed. Congress took this posture because it was avowedly distrustful of the FDA, which had repeatedly failed to interpret the food adulteration provision when applied to dietary supplements as Congress had intended. See S. Rep. No. 103-410 at 2, 14-17, 21-22. Congress has expressly repudiated the usual rules of judicial deference for administrative action that underlie this Court's *Chevron* jurisprudence. That decision of Congress must be fully respected.

Against these weighty institutional considerations, the Respondents offer only the perfunctory assertion that Petitioners' efforts to obtain review of an administrative agency decision necessarily arises under the Administrative Procedure Act to which *Chevron* attaches. That argument conflicts with well settled precedent: When Congress adopts a specific statutory provision that displaces some prior general provision, the specific rules over the general. See *Guidry v. Sheet Metal Workers Nat'l Pension Fund*, 493 U.S. 365, 375-376 (1990). The Tenth Circuit and the Respondents misread *Chevron*, which operates only as a default provision when the particular substantive or enabling statute contains no instructions on how a case is to be resolved. Neither the Tenth Circuit nor Respondents offer a reasoned explanation why they can avoid this explicit statutory command when FDA works through rulemaking. The oversight is especially grievous when the supposed "rulemaking procedure" raises no general principles of FDA law, but is targeted to, as the Respondents concede, a fact-intensive review of a particular record for a single substance. Congress well knew that it was changing the pre-existing law to ensure that FDA could not shield its adulteration decisions from searching judicial review. The law in place when Congress passed DSHEA gave FDA authority to find adulteration through

rulemaking, 21 USC 371(a); thus, we must presume Congress acted intentionally when it chose its unqualified de novo review language. See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000). The Respondents' argument that the Administrative Procedure Act trumps DSHEA's de novo review provision thus fails, indeed even under *Chevron* Step 1, because the statutory language points inexorably in the opposite direction.

The consequences of the Tenth Circuit's rejection of de novo review are profound. Freed from de novo review, the Tenth Circuit never examined the FDA's approach which relied on two forms of proof. First, the Tenth Circuit cites the massive number of complaints filed concerning ephedrine alkaloids without bothering to inquire which, if any, involved proven harm at the usage levels of 10 mgs or less (and none do). See Pet. App. 5-6. Respondents further argue that it would be unethical to run clinical trials at low dose levels as a purported justification for relying on Dr. Inchiosa's hypothetical extrapolation from intravenous drug data. That argument is overwrought because the substance in issue was at all relevant times legally consumed by millions without any scientific evidence of acute or cumulative adverse effects on the cardiovascular system in daily dose amounts of 10 mg or less. See Appellees' App. 283. Consequently, it would be entirely ethical to test this food ingredient at the lower doses. Indeed, FDA permitted and relied upon peer reviewed studies of ephedrine alkaloids at substantially higher doses without noting any ethical reservations. See 69 Fed. Reg. 6788 (Feb. 11, 2004); see also Pet. App. at 92-126 (selected excerpts).

FDA thus depends on Dr. Mario Inchiosa's unpeer-reviewed mathematical extrapolation, which FDA substitutes for real proof that ephedrine alkaloids at 10 mgs or less cause harm. Pet. App. 40, 101. Contrary to Respondents' assertions, Dr. Inchiosa broke with toxicology

conventions by comparing intravenously injected epinephrine (a potent drug) with orally ingested ephedrine alkaloids (a dietary supplement) – chemically distinct entities that affect different organs in different ways. Appellees' App. at 110-111; see also, Brian Hoffman, Catecholamines, Sympathomemetic Drugs, and Adrenergic Receptor Antagonists in Goodman and Gilman's The Pharmacological Basis of Therapeutics 215, 218 (JG Hardman and LE Limbral eds. 2001). Even then, Inchiosa's only concrete finding was that the chronic ingestion of 1.5 mgs of ephedrine alkaloids every four hours would lead to a rise in blood pressure or heart rate. Pet. App. 31. At no point did he establish, or try to establish, that 10 mg of ephedrine alkaloids or less consumed in 5 mg or less tablets twice daily would replicate his hypothesized rise in blood pressure coming from chronic day and night dosing of 1.5 mg every four hours. Evaluated de novo, with the burden of proof on the government, Inchiosa's submission would fail miserably to justify the wholesale ban of ephedrine alkaloids down to a single molecule. Thus, the legal choice of review method affected outcome.

B. THE GOVERNMENT'S EXPLICIT BURDEN OF PROOF UNDER DSHEA REQUIRES A DOSE SPECIFIC, RISK-BASED ASSESSMENT OF ADULTERATION

Respondents seek to avoid the statutory burden of proof, which states that "the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated," 21 USC 342(f)(1), by a manipulated overreading of the substantive phrase in the statute, which speaks of "significant or unreasonable risks" of harm. Their first principal argument, that "unreasonable" in 21 USC 342(f)(1)(A) requires a systematic comparison of risks with benefits, contains a tacit admission. Respondents read the statutory adulteration language for dietary supplements

– "presents a significant or unreasonable risk of illness or injury" – in the disjunctive, so that it becomes possible to find that admittedly insignificant risks can be somehow unreasonable. Yet how can one establish adulteration when risk from a product is insignificant? The FDA's extrastatutory construction of the term "unreasonable" becomes tenable only if FDA, without any findings of fact, concludes by fiat that all the consumer uses of ephedrine alkaloids are worthless for any of the multiple purposes for which those substances are sold and used, such as weight loss, enhanced athletic performance, increased energy levels, and easier breathing. At no point did the FDA seek to compare the benefits of ephedrine alkaloids at low doses against the insignificant risks they produced.

In addition, FDA tortured the statute by separating the word "unreasonable" from the noun it is meant to modify, "risk," and more particularly "risk of illness or injury." As Respondents interpret the statute, an infinitesimal or insignificant risk justifies a finding of adulteration that permits a food to be banned unless the FDA subjectively finds evidence of a substantial health benefit (thereby shifting the burden of proof wrongly back to the manufacturer), by which FDA means a disease treatment effect. See Pet. App. 93 ("only known and reasonably likely [health] benefits" suffice); 94 (proof of risks "can be met with any science-based evidence" and without proof of causality). Yet how is that to be done when FDA explicitly prohibits disease treatment proof for dietary supplements, proof the agency consigns exclusively to the drug category? See *Whitaker*, 353 F.3d at 948-949. By relying on this extrastatutory, unauthorized methodology, FDA ensures that proof of risk at any level will always outweigh benefit. The risk, FDA further insists, need not be shown to be causally related to actual illness or injury. Pet. App. 94. Thus even a single molecule of ephedrine alkaloids for which there is not the slightest proof of harm always creates an "unreasonable

risk" because it is compared to FDA's irrebuttable presumption of insufficient proof of health benefit. Under this bizarre schema, the absence of proof of safety is transmuted into affirmative proof of risk in ways that make a mockery of the statutory burden of proof provision, 21 USC 342(f)(1) (" . . . the United States shall bear the burden of proof on each element to show . . . [adulteration]").

Congress never intended the dietary supplement adulteration provision to be construed in this Kafkaesque way. Congress intended to compel FDA adherence to the existing adulteration statute and standards, which evaluated adulteration based exclusively on risk at recommended doses. See S. Rep. No. 103-410 at 22 ("The committee's amendment will correct [FDA's] abuse by rationalizing the treatment of dietary supplements according to the pattern of the existing statute, and in conformity with the original congressional intent"). A risk is unreasonable under the congressional command only if it can be shown under conditions of actual use to be injurious to health. Dose determines toxicity under this construct and causality is a necessary component. Thus, if a molecule of ephedrine alkaloids is not shown to be injurious to health at the recommended dose, it poses no unreasonable risk and FDA may not ban it. No risk is unreasonable unless it poses a threat to health. Inherent in risk of illness or injury is an assessment of significance. The categorical exclusion of significance by FDA is, then, contrary to the plain and intended meaning of the statute, even of the term "unreasonable risk." A threat to health from a food has long been held extant when the dose of the dietary ingredient in that food can be shown to cause illness or injury. Without causation, the FDA has no distinguishing principle that allows it to discern whether any food or dietary ingredient is adulterated. In the absence of causation, which is dose dependent, all dietary ingredients are adulterated because quite literally nothing remains to distinguish a safe dose of a food from a poisonous one. Thus, under Respondents'

schema, any dietary ingredient the FDA designates as adulterated is adulterated, regardless of dose, causation, or significance of risk. Therein lies the *in terrorem* effect of the Final Rule the Tenth Circuit upheld, an effect that is wreaking havoc in the marketplace. The legislative history plainly contradicts this schema. See S. Rep. No. 103-410 at 22.

Once the Court holds that Congress meant what it said, the rest of this case falls into line without need for any fact by fact appraisal. When it is recognized that de novo review is required, and that the burden of proof is on the government, the flimsy evidence upon which FDA relies condemning 10 mg or less ephedrine alkaloids cannot pass muster. The Respondents seek to reassure this Court that all is well by making the astonishing claim that the 100% absorption achieved for epinephrine by the intravenous injection of that drug is equal to the rate of absorption of ephedrine alkaloids achieved by oral ingestion of that dietary supplement. Resp. Brief in Opp. at 3. The dietary supplement here is raw crushed ephedra sinica herb, found in ephedra tea, classified as a food. The notion that a food bound alkaloid that must pass through the stomach and again the liver is absorbed equally with a purified, intravenously injected drug is indefensible because it offends basic principles of pharmacology and toxicology. See Appellees' App. 100-101; see also Hoffman, supra, 215, 218. That this improper premise undergirds Dr. Inchiosa's unpeer-reviewed hypothetical model offers yet another bit of proof that could never survive scrutiny in a de novo review.

Finally, Respondents err by arguing that the point is established in the works cited by Dr. Inchiosa; in fact, "[i]n no reference cited . . . were both epinephrine and ephedrine injected," Appellees' App. at 110, and one of Inchiosa's key references contradicts his model by demonstrating that even when injected at some levels ephedrine triggers no sympathomemetic responses and by demonstrating that the relationship to epinephrine is not linear. Id. at

112-113. There is further no direct evidence that ephedrine alkaloids when consumed (rather than intravenously injected) have a 1:1 ingestion/absorption ratio. The assumption is flatly unsupported as indeed are the Inchiosa letters upon which FDA relies. Yet FDA depends on them as the exclusive proof of low dose ephedrine toxicity. The petitioners stand ready at trial to prove the truth of all their assertions, and to contradict the many and multiple errors on the facts of this case that are found in the government's brief in opposition to certiorari. But it is not for this Court to weigh these evidentiary matters. It should take certiorari to ensure that the proper standards of review under DSHEA are not blocked by an improper reading of the statute and an unwise extension of *Chevron* to areas that Congress has expressly cordoned off from its application.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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